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(54) Complexes and chelates of azithromycin as antiulcer drugs

Komplexe und Chelate des Azithromycins als Antiulcus-Mittel

Complexes et chélates de l'azithromycine comme agents anti-ulcère

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(56) References cited:
EP-A- 0 206 625
EP-A- 0 259 789
WO-A-86/05981

- **JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, vol. 22, no. 5, 1988, pages 631-636; D. J. HARDY et al.: "Susceptibility of Campylobacter pylori to macrolides and fluoroquinolones"**
- **DIGESTION, vol. 49, suppl. 1, October 1991, pages 36-37; D.E. HERNANDEZ et al.: "Effect of azithromycin kelate in different animal models of peptic ulcer disease"**

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Description

The present invention relates to complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}, processes for the preparation of the present complexes or chelates of azithromyzin, and the use of the present complexes or chelates of azithromycin for the manufacture of a medicament for use in the treatment of ulcers.

It has been known that some organic compounds form metal complexes and chelates, thereby changing their physical-chemical properties (solubility, stability, melting point, etc.) and the pharmacokinetics as well as the pharmacodynamics in biologically active compounds.

There was described (BE Patent 892,357) the formation of Co^{2+} complexes of macrolide antibiotics, especially of erythromycin, the starting substance for obtaining N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (non-proprietary name azithromycin; proprietary name Sumamed ® (PLIVA, Zagreb, Yugoslavia)), whereas J. Pharm. Pharmac. 18, (1966) 727 asserts that with other divalent metal ions (Cu^{2+}, Ca^{2+}, Mg^{2+}, Ni^{2+} and Zn^{2+}) no complexes are formed. On the contrary, we have found that azithromycin forms complexes with bivalent metals yielding products of a high antibiotic activity (HU Patent 198,507).

It has been known that *inter alia* Al-Mg gel is applied as antacid in the treatment of duodenal or gastric ulcer giving relief to the gastric mucosa and keeping the pH of the gastric juice between 4.5 and 5.5. For the same purpose also some antibiotics have been used in order to eradicate the microorganisms *Helicobacter pylori* and *Campylobacter jejuni* which are allegedly one of the factors causing the development and the relapse of duodenal or gastric ulcers. Since it has been presumed that *Helicobacter pylori* inhabits the mucous region of the gastric membrane - whereby the often unsuccessful eradication and the resulting recurrences have been explained - there have been applied ever increasing doses and durations of treatment with various antibiotics. Even azithromycin is no exception.

A subject-matter of the present invention is the use of complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} for the manufacture of a medicament for use in the treatment of ulcers.

Another subject-matter of the present invention are complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}.

A further subject-matter of the present invention is a process for the preparation of complexes or chelates of azithromycin by means of reacting the antibiotic in its free base or salt form, especially hydrochloride, with salts of bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}, especially chlorides, in a ratio of 2:1, at room temperature, in aqueous solution or in a mixture of water/alcohol, at a pH of 8.0 - 11.0, or with metal hydroxides and/or carbonates, subsalicylates or their gels, which are used as antacids such as aluminium hydroxide-magnesium carbonate and sucralfate, in a ratio of 1:1 to 1:4 in an alcohol. The process is most suitably performed with the antibiotic base in alcohol such as methanol or ethanol. The product is isolated in a conventional manner, e.g. by evaporation of the solvent (alcohol) from the reaction mixture under reduced pressure and the isolation of the product by means of filtration.

The product is formulated by known methods into pharmaceuticals such as granules or chewing tablets or aqueous suspensions.

It has been found that the azithromycin chelates with aluminium and magnesium in a ratio of 1:1 to 1:4, in the form of gels as well as with other gels, which are applied as antacids, are retained within 24 hours in the mucous region of the rat stomach in a 1.5-to 60-fold concentrations (Tables 1 and 2), which exceed the Minimal Inhibitory and Bactericidal Concentrations for *Helicobacter pylori* and *Campylobacter jejuni*; accordingly, said preparations are more indicated for the treatment of gastric diseases such as gastric or duodenal ulcers than the parent azithromycin. Furtheron, it has been demonstrated by toxicological investigations that the pharmaceutical formulations do not change the toxicity of the active ingredient.

TABLE 1

Concentration of azithromycin in the rat gastric mucosa upon one administration of 60 mg/rat p.o. of
- azithromycin Al-Mg gel 1:1
- azithromycin sucralfate gel 1:1 in comparison with
- azithromycin bi-subsalicylate gel 1:1 and
azithromycin (30 mg/rat p.o)

Time h	Azithromycin Al-Mg gel µg/g of tissue	Azithromycin sucralfate µg/g of tissue	Azithromycin bi-subsalicylate µg/g of tissue	Azithromycin µg/g of tissue
5	$\bar{X}$ = 159.4 ± 28.66	$\bar{X}$ = 100.2 ± 32.94	$\bar{X}$ = 32.5 ± 8.60	$\bar{X}$ = 99.4 ± 16.61
18	$\bar{X}$ = 107.4 ± 32.04	$\bar{X}$ = 75.1 ± 21.54	$\bar{X}$ = 31.3 ± 10.02	$\bar{X}$ = 98.3 ± 30.71
24	$\bar{X}$ = 71.8 ± 20.41	$\bar{X}$ = 74.5 ± 33.45	$\bar{X}$ = 26.1 ± 5.26	$\bar{X}$ = 1.3 ± 0.08
32	$\bar{X}$ = 7.9 ± 2.88	$\bar{X}$ = 36.6 ± 7.53	$\bar{X}$ = 21.1 ± 3.90	$\bar{X}$ = 0

TABLE 2

Concentration of azithromycin in the rat duodenal mucosa upon one administration of 60 mg/rat p.o. of
- azithromycin Al-Mg gel 1:1
- azithromycin sucralfate gel 1:1 in comparison with
- azithromycin bi-subsalicylate gel 1:1 and

azithromycin (30 mg/rat p.o.)

Time h	Azithromycin Al-Mg gel µg/g of tissue	Azithromycin sucralfate µg/g of tissue	Azithromycin bi-subsalicylate µg/g of tissue	Azithromycin µg/g of tissue
5	$\bar{X}$ = 90.0 ± 14.78	$\bar{X}$ = 98.1 ± 14.17	$\bar{X}$ = 73.8 ± 20.77	$\bar{X}$ = 103.5 ± 7.35
18	$\bar{X}$ = 91.3 ± 13.46	$\bar{X}$ = 82.8 ± 27.11	$\bar{X}$ = 62.2 ± 20.55	$\bar{X}$ = 86.1 ± 33.45
24	$\bar{X}$ = 74.3 ± 29.00	$\bar{X}$ = 55.8 ± 17.04	$\bar{X}$ = 40.5 ± 13.33	$\bar{X}$ = 0
32	$\bar{X}$ = 7.6 ± 1.07	$\bar{X}$ = 35.6 ± 18.87	$\bar{X}$ = 42.4 ± 11.25	$\bar{X}$ = 0

The invention is illustrated by the following Examples:

Example 1

In 50 mL (0.02 mole) of a solution of azithromycin in 95% ethanol there were dissolved 0.067 g $AlCl_3$ (0.01 M solution with respect to Al^{+3}) and upon adjusting the pH value to 8.6 with 0.1 N NaOH it was kept stirring for 1 hour at room temperature in a nitrogen stream. Upon addition of 30 mL water the reaction mixture was evaporated under reduced pressure to about half its volume, whereupon it was kept stirring for two hours and the pH was kept constant (pH state)

at 8.9 with 0.1 N NaOH. The white precipitate was aspirated, washed with 3 x 10 mL of water and dried, yielding 0.68 g of the product (89.0%), m.p. 125-128 °C.

Analysis: Al (atomic absorption spectrometry method):	
Calc.:	1.77%
Found:	1.73%

Activity: 852 E/mg *Sarcina lutea* ATCC 9341

Example 2

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.136 g $FeCl_3 \times 6\ H_2O$ and the pH was kept at 9.0, there was obtained 0.72 g of a light grey product (92.5%); m.p. 130-133 °C.

Analysis: Fe (atomic absorption spectrometry method):	
Calc.:	3.59%
Found:	3.71%

Activity: 840 E/mg *Sarcina lutea* ATCC 9341

Example 3

0.750 g of azithromycin were charged into a 100 mL flask and dissolved in 50 mL of water under the addition of 1 N HCl (pH approx. 6.0). Subsequently, there were added 0.136 g $FeCl_3 \times 6\ H_2O$ and it was kept stirring upon gradually adjusting the pH value to 8.9 with 0.1 N NaOH. The reaction mixture was kept stirring for 2 hours at a constant pH value, whereupon the light grey product was aspirated, washed with 3 x 10 mL of water, and dried. There was obtained 0.70 g of the product (89.9%). The analysis of the product was identical as in Example 2.

Example 4

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.132 g $RhCl_3 \times 3\ H_2O$ there was obtained 0.67 g of a light grey product (83.6%); m.p. 120-123 °C.

Analysis : Rh (polarographic method; 1 M pyridine - 1 M KCl, $E_{1/2}$ = -0.40 V; SCE (Saturated Calomel Electrode)	
Calc.:	6.42%
Found:	6.15%

Activity: 834 E/mg *Sarcina lutea* ATCC 9341

Example 5

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.186 g of $LaCl_3 \times 7\ H_2O$ and the pH was kept at 9.2, there was obtained 0.66 g of a white product (80.5%); m.p. 118-122 °C.

Analysis: La (atomic absorption spectrometry method):	
Calc.:	8.47%
Found:	8.10%

Activity: 830 E/mg *Sarcina lutea* ATCC 9341

Reference Example

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.158 g of $BiCl_3$, there was obtained 0.70 g of a product (82.0%).

Analysis: Bi (atomic absorption spectrometry method):	
Calc.:	12.25%
Found:	12.00%

Activity: 812 E/mg *Sarcina lutea* ATCC 9341

Example 6

In accordance with the process described in Example 3 with the sole exception that $FeCl_3$ was replaced by the addition of 0.102 g $MgCl_2 \times 6\ H_2O$ and the pH was kept at 8.6, there was obtained 0.55 g (75.0%) of a white product.

Analysis: Mg (atomic absorption spectrometry method):	
Calc.:	1.22%
Found:	1.54%

Activity: 850 E/mg *Sarcina lutea* ATCC 9341

Example 7

5.0 g of azithromycin were charged into a 100 mL flask and dissolved in 50 mL of methanol. Upon the addition of 5.0 g of aluminium hydroxide-magnesium carbonate gel it was kept stirring for 2 hours in a nitrogen stream. The suspension was then evaporated to dryness under reduced pressure and the obtained product (9.5 g) was air-dried.

Activity: 430 E/mg *Sarcina lutea* ATCC 9341

Example 8

In accordance with the process described in Example 8 with the sole exception that 5.0 g of aluminium hydroxide-magnesium carbonate gel were replaced by 10.0 g thereof and that there were used 100 mL of 95% ethanol instead of methanol, there were obtained 14.3 g of the product.
Activity: 295 E/mg *Sarcina lutea* ATCC 9341

Example 9

In accordance with the process described in Example 8 with the sole exception that 5.0 g of aluminium hydroxide-magnesium carbonate gel were replaced by 20.0 g thereof, there were obtained 23.5 g of the product.
Activity: 160 E/mg *Sarcina lutea* ATCC 9341

Example 10

In accordance with the process described in Example 8 with the sole exception that aluminium hydroxide-magnesium carbonate gel was replaced by 5.0 g of sucralfate, there were obtained 9.5 g of the product.
Activity: 435 E/mg *Sarcina lutea* ATCC 9341

Example 11

In accordance with the process described in Example 8 with the sole exception that aluminium hydroxide-magnesium carbonate gel was replaced by 5.0 g of bismuth subsalicylate, there were obtained 9.3 g of the product.
Activity: 420 E/mg *Sarcina lutea* ATCC 9341

Claims

1. The use of complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} for the manufacture of a medicament for use in the treatment of ulcers.

2. The use according to Claim 1, of chelates of azithromycin with antacids chosen from the group of salts of Al and Mg in the form of gels.

3. The use according to Claim 2, of chelates of azithromycin with aluminium hydroxide-magnesium carbonate in the form of gels.

4. The use according to Claim 2, of chelates of azithromycin with sucralfate in the form of gels.

5. Complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}

6. Complexes or chelates of azithromycin with antacids chosen from the group of salts of Al and Mg in the form of gels.

7. A chelate of azithromycin with aluminium hydroxide-magnesium carbonate in the form of gels.

8. A chelate of azithromycin with sucralfate in the form of gels.

9. A complex of azithromycin with Mg^{2+}.

10. A complex of azithromycin with Al^{3+}.

11. A complex of azithromycin with Fe^{3+}.

12. A complex of azithromycin with Rh^{3+}.

13. A complex of azithromycin with La^{3+}.

14. Chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} in the ratio of 1:1 to 1:4.

15. Complexes of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} in the ratio of 2:1.

16. A process for the preparation of complexes or chelates of azithromycin by means of reacting the antibiotic in its free base or salt form, with salts of bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} in a ratio of 2:1, at room temperature, in an aqueous solution or a mixture of water/alcohol, at a pH of 8.0 - 11.0, or with metal hydroxides and/or carbonates, subsalicylates or their gels, in a ratio of 1:1 to 1:4, in an alcohol.

Patentansprüche

1. Verwendung von Komplexen oder Chelaten des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} zur Herstellung eines Arzneimittels zur Verwendung in der Behandlung von Ulzera.

2. Verwendung gemäss Anspruch 1 von Chelaten des Azithromycins mit Antacida ausgewählt aus der Gruppe von Al- und Mg- Salzen in der Form von Gelen.

3. Verwendung gemäss Anspruch 2 von Chelaten des Azithromycins mit Aluminiumhydroxid-Magnesiumcarbonat in der Form von Gelen.

4. Verwendung gemäss Anspruch 2 von Chelaten des Azithromycins mit Sucralfat in der Form von Gelen.

5. Komplexe oder Chelate des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+}.

6. Komplexe oder Chelate des Azithromycins mit Antacida ausgewählt aus der Gruppe von Al- und Mg- Salzen in der Form von Gelen.

7. Chelat des Azithromycins mit Aluminiumhydroxid-Magnesiumcarbonat in der Form von Gelen.

8. Chelat des Azithromycins mit Sucralfat in der Form von Gelen.

9. Komplex des Azithromycins mit Mg^{2+}.

10. Komplex des Azithromycins mit Al^{3+}.

11. Komplex des Azithromycins mit Fe^{3+}.

12. Komplex des Azithromycins mit Rh^{3+}.

13. Komplex des Azithromycins mit La^{3+}.

14. Chelate des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} im Verhältnis von 1:1 bis 1:4.

15. Komplexe des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} im Verhältnis 2:1.

16. Verfahren zur Herstellung von Komplexen oder Chelaten des Azithromycins mittels Umsetzung des Antibiotikums in der Form einer freien Base oder in Salzform mit Salzen von zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} in einem Verhältnis 2:1 bei Zimmertemperatur in einer wässrigen Lösung oder einer Mischung von Wasser/Alkohol und bei einem pH von 8,0 - 11,0, oder mit Metallhydroxiden und/oder -carbonaten, -subsalicylaten oder deren Gelen in einem Verhältnis von 1:1 bis 1:4 in einem Alkohol.

Revendications

1. Utilisation de complexes ou de chélates de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} pour la fabrication d'un médicament destiné au traitement d'ulcères.

2. Utilisation suivant la revendication 1 de chélates de l'azithromycine avec des anti-acides choisis dans le groupe formé par les sels d'Al et de Mg sous la forme de gels.

3. Utilisation suivant la revendication 2 de chélates de l'azithromycine avec de l'hydroxyde d'aluminium - carbonate de magnésium sous la forme de gels.

4. Utilisation suivant la revendication 2 de chélates de l'azithromycine avec du sucralfate sous la forme de gels.

5. Complexes ou chélates de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+}.

6. Complexes ou chélates de l'azithromycine avec des anti-acides choisis dans le groupe formé par les sels d'Al et de Mg sous la forme de gels.

7. Chélate de l'azithromycine avec de l'hydroxyde d'aluminium - carbonate de magnésium sous la forme de gels.

8. Chélate de l'azithromycine avec du sucralfate sous la forme de gels.

9. Complexe de l'azithromycine avec Mg^{2+}.

10. Complexe de l'azithromycine avec Al^{3+}.

11. Complexe de l'azithromycine avec Fe^{3+}.

12. Complexe de l'azithromycine avec Rh^{3+}.

13. Complexe de l'azithromycine avec La^{3+}.

14. Chélates de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} dans le rapport de 1:1 à 1:4.

15. Complexes de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} dans le rapport de 2:1.

16. Procédé de préparation de complexes ou de chélates de l'azithromycine par la réaction de l'antibiotique sous la forme de sa base libre ou sous la forme de sel, avec des sels de métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} dans le rapport de 2:1, à la température ambiante, dans une solution aqueuse ou un mélange d'eau/alcool, à un pH de 8,0 - 11,0, ou avec des hydroxydes et/ou carbonates de métaux, des sub-salicylates ou leurs gels, dans un rapport de 1:1 à 1:4, dans un alcool.

Description

The present invention relates to complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}, processes for the preparation of the present complexes or chelates of azithromyzin, and the use of the present complexes or chelates of azithromycin for the manufacture of a medicament for use in the treatment of ulcers.

It has been known that some organic compounds form metal complexes and chelates, thereby changing their physical-chemical properties (solubility, stability, melting point, etc.) and the pharmacokinetics as well as the pharmacodynamics in biologically active compounds.

There was described (BE Patent 892,357) the formation of Co^{2+} complexes of macrolide antibiotics, especially of erythromycin, the starting substance for obtaining N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (non-proprietary name azithromycin; proprietary name Sumamed ® (PLIVA, Zagreb, Yugoslavia)), whereas J. Pharm. Pharmac. 18, (1966) 727 asserts that with other divalent metal ions (Cu^{2+}, Ca^{2+}, Mg^{2+}, Ni^{2+} and Zn^{2+}) no complexes are formed. On the contrary, we have found that azithromycin forms complexes with bivalent metals yielding products of a high antibiotic activity (HU Patent 198,507).

It has been known that *inter alia* Al-Mg gel is applied as antacid in the treatment of duodenal or gastric ulcer giving relief to the gastric mucosa and keeping the pH of the gastric juice between 4.5 and 5.5. For the same purpose also some antibiotics have been used in order to eradicate the microorganisms *Helicobacter pylori* and *Campylobacter jejuni* which are allegedly one of the factors causing the development and the relapse of duodenal or gastric ulcers. Since it has been presumed that *Helicobacter pylori* inhabits the mucous region of the gastric membrane - whereby the often unsuccessful eradication and the resulting recurrences have been explained - there have been applied ever increasing doses and durations of treatment with various antibiotics. Even azithromycin is no exception.

A subject-matter of the present invention is the use of complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} for the manufacture of a medicament for use in the treatment of ulcers.

Another subject-matter of the present invention are complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}.

A further subject-matter of the present invention is a process for the preparation of complexes or chelates of azithromycin by means of reacting the antibiotic in its free base or salt form, especially hydrochloride, with salts of bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}, especially chlorides, in a ratio of 2:1, at room temperature, in aqueous solution or in a mixture of water/alcohol, at a pH of 8.0 - 11.0, or with metal hydroxides and/or carbonates, subsalicylates or their gels, which are used as antacids such as aluminium hydroxide-magnesium carbonate and sucralfate, in a ratio of 1:1 to 1:4 in an alcohol. The process is most suitably performed with the antibiotic base in alcohol such as methanol or ethanol. The product is isolated in a conventional manner, e.g. by evaporation of the solvent (alcohol) from the reaction mixture under reduced pressure and the isolation of the product by means of filtration.

The product is formulated by known methods into pharmaceuticals such as granules or chewing tablets or aqueous suspensions.

It has been found that the azithromycin chelates with aluminium and magnesium in a ratio of 1:1 to 1:4, in the form of gels as well as with other gels, which are applied as antacids, are retained within 24 hours in the mucous region of the rat stomach in a 1.5-to 60-fold concentrations (Tables 1 and 2), which exceed the Minimal Inhibitory and Bactericidal Concentrations for *Helicobacter pylori* and *Campylobacter jejuni*; accordingly, said preparations are more indicated for the treatment of gastric diseases such as gastric or duodenal ulcers than the parent azithromycin. Furtheron, it has been demonstrated by toxicological investigations that the pharmaceutical formulations do not change the toxicity of the active ingredient.

TABLE 1

Concentration of azithromycin in the rat gastric mucosa upon one administration of 60 mg/rat p.o. of
- azithromycin Al-Mg gel 1:1
- azithromycin sucralfate gel 1:1 in comparison with
- azithromycin bi-subsalicylate gel 1:1 and
azithromycin (30 mg/rat p.o)

Time h	Azithromycin Al-Mg gel µg/g of tissue	Azithromycin sucralfate µg/g of tissue	Azithromycin bi-subsalicylate µg/g of tissue	Azithromycin µg/g of tissue
5	$\bar{X}$ = 159.4 ± 28.66	$\bar{X}$ = 100.2 ± 32.94	$\bar{X}$ = 32.5 ± 8.60	$\bar{X}$ = 99.4 ± 16.61
18	$\bar{X}$ = 107.4 ± 32.04	$\bar{X}$ = 75.1 ± 21.54	$\bar{X}$ = 31.3 ± 10.02	$\bar{X}$ = 98.3 ± 30.71
24	$\bar{X}$ = 71.8 ± 20.41	$\bar{X}$ = 74.5 ± 33.45	$\bar{X}$ = 26.1 ± 5.26	$\bar{X}$ = 1.3 ± 0.08
32	$\bar{X}$ = 7.9 ± 2.88	$\bar{X}$ = 36.6 ± 7.53	$\bar{X}$ = 21.1 ± 3.90	$\bar{X}$ = 0

TABLE 2

Concentration of azithromycin in the rat duodenal mucosa upon one administration of 60 mg/rat p.o. of

- azithromycin Al-Mg gel 1:1
- azithromycin sucralfate gel 1:1 in comparison with
- azithromycin bi-subsalicylate gel 1:1 and

azithromycin (30 mg/rat p.o).

Time h	Azithromycin Al-Mg gel µg/g of tissue	Azithromycin sucralfate µg/g of tissue	Azithromycin bi-subsalicylate µg/g of tissue	Azithromycin µg/g of tissue
5	$\bar{X}$ = 90.0 ± 14.78	$\bar{X}$ = 98.1 ± 14.17	$\bar{X}$ = 73.8 ± 20.77	$\bar{X}$ = 103.5 ± 7.35
18	$\bar{X}$ = 91.3 ± 13.46	$\bar{X}$ = 82.8 ± 27.11	$\bar{X}$ = 62.2 ± 20.55	$\bar{X}$ = 86.1 ± 33.45
24	$\bar{X}$ = 74.3 ± 29.00	$\bar{X}$ = 55.8 ± 17.04	$\bar{X}$ = 40.5 ± 13.33	$\bar{X}$ = 0
32	$\bar{X}$ = 7.6 ± 1.07	$\bar{X}$ = 35.6 ± 18.87	$\bar{X}$ = 42.4 ± 11.25	$\bar{X}$ = 0

The invention is illustrated by the following Examples:

Example 1

In 50 mL (0.02 mole) of a solution of azithromycin in 95% ethanol there were dissolved 0.067 g $AlCl_3$ (0.01 M solution with respect to Al^{+3}) and upon adjusting the pH value to 8.6 with 0.1 N NaOH it was kept stirring for 1 hour at room temperature in a nitrogen stream. Upon addition of 30 mL water the reaction mixture was evaporated under reduced pressure to about half its volume, whereupon it was kept stirring for two hours and the pH was kept constant (pH state)

at 8.9 with 0.1 N NaOH. The white precipitate was aspirated, washed with 3 x 10 mL of water and dried, yielding 0.68 g of the product (89.0%), m.p. 125-128 °C.

Analysis: Al (atomic absorption spectrometry method):	
Calc.:	1.77%
Found:	1.73%

Activity: 852 E/mg *Sarcina lutea* ATCC 9341

Example 2

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.136 g $FeCl_3 \times 6\ H_2O$ and the pH was kept at 9.0, there was obtained 0.72 g of a light grey product (92.5%); m.p. 130-133 °C.

Analysis: Fe (atomic absorption spectrometry method):	
Calc.:	3.59%
Found:	3.71%

Activity: 840 E/mg *Sarcina lutea* ATCC 9341

Example 3

0.750 g of azithromycin were charged into a 100 mL flask and dissolved in 50 mL of water under the addition of 1 N HCl (pH approx. 6.0). Subsequently, there were added 0.136 g $FeCl_3 \times 6\ H_2O$ and it was kept stirring upon gradually adjusting the pH value to 8.9 with 0.1 N NaOH. The reaction mixture was kept stirring for 2 hours at a constant pH value, whereupon the light grey product was aspirated, washed with 3 x 10 mL of water, and dried. There was obtained 0.70 g of the product (89.9%). The analysis of the product was identical as in Example 2.

Example 4

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.132 g $RhCl_3 \times 3\ H_2O$ there was obtained 0.67 g of a light grey product (83.6%); m.p. 120-123 °C.

Analysis : Rh (polarographic method; 1 M pyridine - 1 M KCl, $E_{1/2}$ = -0.40 V; SCE (Saturated Calomel Electrode)	
Calc.:	6.42%
Found:	6.15%

Activity: 834 E/mg *Sarcina lutea* ATCC 9341

Example 5

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.186 g of $LaCl_3 \times 7\ H_2O$ and the pH was kept at 9.2, there was obtained 0.66 g of a white product (80.5%); m.p. 118-122 °C.

Analysis: La (atomic absorption spectrometry method):	
Calc.:	8.47%
Found:	8.10%

Activity: 830 E/mg *Sarcina lutea* ATCC 9341

Reference Example

In accordance with the process described in Example 1 with the sole exception that $AlCl_3$ was replaced by the addition of 0.158 g of $BiCl_3$, there was obtained 0.70 g of a product (82.0%).

Analysis: Bi (atomic absorption spectrometry method):	
Calc.:	12.25%
Found:	12.00%

Activity: 812 E/mg *Sarcina lutea* ATCC 9341

Example 6

In accordance with the process described in Example 3 with the sole exception that $FeCl_3$ was replaced by the addition of 0.102 g $MgCl_2 \times 6\ H_2O$ and the pH was kept at 8.6, there was obtained 0.55 g (75.0%) of a white product.

Analysis: Mg (atomic absorption spectrometry method):	
Calc.:	1.22%
Found:	1.54%

Activity: 850 E/mg *Sarcina lutea* ATCC 9341

Example 7

5.0 g of azithromycin were charged into a 100 mL flask and dissolved in 50 mL of methanol. Upon the addition of 5.0 g of aluminium hydroxide-magnesium carbonate gel it was kept stirring for 2 hours in a nitrogen stream. The suspension was then evaporated to dryness under reduced pressure and the obtained product (9.5 g) was air-dried.

Activity: 430 E/mg *Sarcina lutea* ATCC 9341

Example 8

In accordance with the process described in Example 8 with the sole exception that 5.0 g of aluminium hydroxide-magnesium carbonate gel were replaced by 10.0 g thereof and that there were used 100 mL of 95% ethanol instead of methanol, there were obtained 14.3 g of the product.

Activity: 295 E/mg *Sarcina lutea* ATCC 9341

Example 9

In accordance with the process described in Example 8 with the sole exception that 5.0 g of aluminium hydroxide-magnesium carbonate gel were replaced by 20.0 g thereof, there were obtained 23.5 g of the product.

Activity: 160 E/mg *Sarcina lutea* ATCC 9341

Example 10

In accordance with the process described in Example 8 with the sole exception that aluminium hydroxide-magnesium carbonate gel was replaced by 5.0 g of sucralfate, there were obtained 9.5 g of the product.

Activity: 435 E/mg *Sarcina lutea* ATCC 9341

Example 11

In accordance with the process described in Example 8 with the sole exception that aluminium hydroxide-magnesium carbonate gel was replaced by 5.0 g of bismuth subsalicylate, there were obtained 9.3 g of the product.

Activity: 420 E/mg *Sarcina lutea* ATCC 9341

Claims

1. The use of complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} for the manufacture of a medicament for use in the treatment of ulcers.

2. The use according to Claim 1, of chelates of azithromycin with antacids chosen from the group of salts of Al and Mg in the form of gels.

3. The use according to Claim 2, of chelates of azithromycin with aluminium hydroxide-magnesium carbonate in the form of gels.

4. The use according to Claim 2, of chelates of azithromycin with sucralfate in the form of gels.

5. Complexes or chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+}

6. Complexes or chelates of azithromycin with antacids chosen from the group of salts of Al and Mg in the form of gels.

7. A chelate of azithromycin with aluminium hydroxide-magnesium carbonate in the form of gels.

8. A chelate of azithromycin with sucralfate in the form of gels.

9. A complex of azithromycin with Mg^{2+}.

10. A complex of azithromycin with Al^{3+}.

11. A complex of azithromycin with Fe^{3+}.

12. A complex of azithromycin with Rh^{3+}.

13. A complex of azithromycin with La^{3+}.

14. Chelates of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} in the ratio of 1:1 to 1:4.

15. Complexes of azithromycin with bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} in the ratio of 2:1.

16. A process for the preparation of complexes or chelates of azithromycin by means of reacting the antibiotic in its free base or salt form, with salts of bivalent and/or trivalent metals chosen from Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} and La^{3+} in a ratio of 2:1, at room temperature, in an aqueous solution or a mixture of water/alcohol, at a pH of 8.0 - 11.0, or with metal hydroxides and/or carbonates, subsalicylates or their gels, in a ratio of 1:1 to 1:4, in an alcohol.

Patentansprüche

1. Verwendung von Komplexen oder Chelaten des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} zur Herstellung eines Arzneimittels zur Verwendung in der Behandlung von Ulzera.

2. Verwendung gemäss Anspruch 1 von Chelaten des Azithromycins mit Antacida ausgewählt aus der Gruppe von Al- und Mg- Salzen in der Form von Gelen.

3. Verwendung gemäss Anspruch 2 von Chelaten des Azithromycins mit Aluminiumhydroxid-Magnesiumcarbonat in der Form von Gelen.

4. Verwendung gemäss Anspruch 2 von Chelaten des Azithromycins mit Sucralfat in der Form von Gelen.

5. Komplexe oder Chelate des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+}.

6. Komplexe oder Chelate des Azithromycins mit Antacida ausgewählt aus der Gruppe von Al- und Mg- Salzen in der Form von Gelen.

7. Chelat des Azithromycins mit Aluminiumhydroxid-Magnesiumcarbonat in der Form von Gelen.

8. Chelat des Azithromycins mit Sucralfat in der Form von Gelen.

9. Komplex des Azithromycins mit Mg^{2+}.

10. Komplex des Azithromycins mit Al^{3+}.

11. Komplex des Azithromycins mit Fe^{3+}.

12. Komplex des Azithromycins mit Rh^{3+}.

13. Komplex des Azithromycins mit La^{3+}.

14. Chelate des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} im Verhältnis von 1:1 bis 1:4.

15. Komplexe des Azithromycins mit zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} im Verhältnis 2:1.

16. Verfahren zur Herstellung von Komplexen oder Chelaten des Azithromycins mittels Umsetzung des Antibiotikums in der Form einer freien Base oder in Salzform mit Salzen von zweiwertigen und/oder dreiwertigen Metallen ausgewählt aus Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} und La^{3+} in einem Verhältnis 2:1 bei Zimmertemperatur in einer wässrigen Lösung oder einer Mischung von Wasser/Alkohol und bei einem pH von 8,0 - 11,0, oder mit Metallhydroxiden und/oder -carbonaten, -subsalicylaten oder deren Gelen in einem Verhältnis von 1:1 bis 1:4 in einem Alkohol.

Revendications

1. Utilisation de complexes ou de chélates de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} pour la fabrication d'un médicament destiné au traitement d'ulcères.

2. Utilisation suivant la revendication 1 de chélates de l'azithromycine avec des anti-acides choisis dans le groupe formé par les sels d'Al et de Mg sous la forme de gels.

3. Utilisation suivant la revendication 2 de chélates de l'azithromycine avec de l'hydroxyde d'aluminium - carbonate de magnésium sous la forme de gels.

4. Utilisation suivant la revendication 2 de chélates de l'azithromycine avec du sucralfate sous la forme de gels.

5. Complexes ou chélates de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+}.

6. Complexes ou chélates de l'azithromycine avec des anti-acides choisis dans le groupe formé par les sels d'Al et de Mg sous la forme de gels.

7. Chélate de l'azithromycine avec de l'hydroxyde d'aluminium - carbonate de magnésium sous la forme de gels.

8. Chélate de l'azithromycine avec du sucralfate sous la forme de gels.

9. Complexe de l'azithromycine avec Mg^{2+}.

10. Complexe de l'azithromycine avec Al^{3+}.

11. Complexe de l'azithromycine avec Fe^{3+}.

12. Complexe de l'azithromycine avec Rh^{3+}.

13. Complexe de l'azithromycine avec La^{3+}.

14. Chélates de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} dans le rapport de 1:1 à 1:4.

15. Complexes de l'azithromycine avec des métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} dans le rapport de 2:1.

16. Procédé de préparation de complexes ou de chélates de l'azithromycine par la réaction de l'antibiotique sous la forme de sa base libre ou sous la forme de sel, avec des sels de métaux bivalents et/ou trivalents choisis parmi Mg^{2+}, Al^{3+}, Fe^{3+}, Rh^{3+} et La^{3+} dans le rapport de 2:1, à la température ambiante, dans une solution aqueuse ou un mélange d'eau/alcool, à un pH de 8,0 - 11,0, ou avec des hydroxydes et/ou carbonates de métaux, des subsalicylates ou leurs gels, dans un rapport de 1:1 à 1:4, dans un alcool.